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Hemostatic Agents
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Hemostasis: As you probably remember from your basic science courses, hemostasis begins with damage to tissues. The first phase is the vascular phase in which you have vasoconstriction, which decreases the amount of blood flow to the area. The damage to the vascular endothelium exposes collagen, which then causes platelet aggregation and adhesion. These platelets release various clotting factors, which I will talk about in more detail shortly and initiates the clotting cascade and clot formation. This is followed by a clot retraction phase and finally a clot destruction phase in which plasminogen is converted to plasmin which then causes clot lysis. Of note this patient was taking Amicar, an agent that inhibits the conversion of plasminogen to plasmin and thus helps stabilize clots.

The clotting cascade traditionally is broken up into two basic pathways, the intrinsic pathway and the extrinsic pathway. The intrinsic pathway is primarily activated as we said before by collagen, which is exposed and then it binds factor XII and initiates this entire cascade. In addition, collagen attacks platelets, which then subsequently become activated with the use of several other different cofactors. They release various factors as well. The extrinsic pathway is stimulated by tissue factor, which is exposed by the tissue injury and through factor VII activation, stimulates this pathway. These two pathways then converge in a common pathway where thrombin converts fibrinogen to fibrin monomers, which are then cross linked with the aid of factor XIII and calcium to form fiber polymer and thus clot. The hemostatic agents have been around for a very long time. There is a report that the Egyptians used various high temperature cautery and waxes and poultices on wounds in order to stop bleeding. There are reports that Native Americans also use scrapping on the inside of animal hides and applied those to wounds. The Greek scholar, Hippocrates, described the use of high temperature cautery as well as various topical hemostatic agents and Celsus, the Roman philosopher and physician who gave us the concept of dolor, color, rubor also described the use of various stypticand high temperature cautery and ligation in order to stop bleeding. In the more modern era, the idea of fibrin used as a topical hemostatic agent was introduced in the early 1900s and Gelfoam was introduced in the 1940s and used in neurosurgical procedures.

So what do we want in a good hemostatic agent? First, the ideal hemostatic agent would of course be such that the agent itself is as well as any of its metabolic breakdown products would be safe to use within the body. Secind, you want it to work and you want it to be efficacious.

The definition of efficacy can vary between the different uses, for example a vascular surgeon may want something that polymerizes very quickly in order to stop bleeding, but does not cause clot of the vessel that they spent all this time anastomosing, where as a reconstructive surgeon for example may want something that polymerizes very slowly to give them time to reposition their flaps or grafts.

Third is usability; you want something that is easy to use and that you can use in a variety of different circumstances. Fourth is affordability. This may be more relevant to a hospital administrator or pharmacist who actually does the purchasing, but it impacts the

surgeon because that determines what you have available to you in the operating room. And finally, fifth, approvability. Any of these agents need to be approved by the FDA in order to be used in the US. So the different types of hemostatic agents, which I will be addressing in this talk are listed below and I am going to go through each one of these specifically.

Gelatin sponge or Gelfoam®, which is also known as commercially as Surgifoam again was first introduced in the 1940s by Dr. Gray in the neurosurgical procedures. What it is is purified pork skin gelatin which you can kind think of like Jello®, as it is the same thing that Jello® is made out of.

As you can see on this microscopic view, it has a very amorphous form and has a lot of air spaces and it stains very eosinophilic on H&E stain. Basically the way it works is that its surface essentially acts in the intrinsic pathway causing contact activation and thus platelets. Since it works very proximally within this cascade, you have to have functioning cofactors or clotting factors in order for this to work in helping create clot. Of note, it does absorb approximately 45 times its weight in blood and can expand to approximately 200% of its initial volume. It is absorbed in approximately four to six weeks and on the nasal mucosa it liquifies within two to five days. In the case presentation, this child was initially packed with Gelfoam® approximately a week prior to the time she was seen in the ER and at that point there was no evidence of any Gelfoam left within her nasal cavity. Now the way Gelfoam® can be used, you can either apply dry, directly to the bleeding surface and hold pressure over it or you can wet it in saline and then squeeze out all the air bubbles and use it that way.

Oxidized regenerated cellulose is also known as Surgicel or Oxycel in its commercial forms. It is derived from alpha-cellulose that is actually plant-based. As you can see on microscopic view, Surgicel comes in knit formwhere as Oxycel comes in a microfibrillar form and on microscopic view Surgicel has these fibers which are knit together and they are solid fibers whereas Oxycel has the hollow fibers but they essentially work the same way. Surgicel is relatively acidic and is thought to cause some small vessel contraction. Like Gelfoam, it works at the same point in the intrinsic pathway of clotting causing contact activation. So again the same thing holds that functional clotting factors are needed in order for this to work. It is thought to berelatively bacteriostatic when compared to other hemostatic agents. The theory behind this is that because of its relatively low pH, it deactivates and denatures some of the bacterial proteins especially those related to antibiotic resistance, thus making them more susceptible to antibiotics. It needs to be applied dry and absorbs within four to eight weeks. Of note, on postop imaging Surgicel sometimes causes a ring-enhancing lesion as you can see here on postop imaging, which can be mistaken for an abscess cavity or tumor recurrence. That is something to keep in mind if you are imaging a patient within two months of having operated on them and Surgicel was used during the procedure. On microscopic view, you can see a giant cell reaction.

Our next agent is microfibrillar collagen commercially known as Avitene ®. It is most commonly used in a light flour form, but it does also come in a non-woven web form. This is collagen, which is derived from bovine skin. Under the microscope it is very eosinophilic and of note, under polarizing light it does have periodicity. It binds tightly to blood surfaces, so you do not actually need to achieve a relatively dry field in order to apply it. It causes minimal swelling especially when compared to Gelfoam ®. T he way it works is slightly different because in addition to being collagen and causing contact activation, it does somehow directly activate platelets. But again, it works very proximally within the intrinsic pathway. It is absorbed in three months and it needs to be applied dry.

Collagen sponges, these come in a wide variety of different commercial forms. Again it is similar to Avitene ® and it is derived from bovine Achilles tendon or bovine skin and it works in basically the exact same way as Avitene works and it absorbs in 8-10 weeks.

The next class of hemostatic agents is slightly different: topical thrombin. The idea of topical thrombin has been around since the early 1900s in order to try to achieve clot and in addition the idea of using topical thrombin plus other hemostatic agents such as Gelfoam ® has been around for quite a longtime. In 1999 a new agent was introduced called Floseal™ which basically consists of bovine thrombin plus cross-linked gelatin

granules mixed together. So the way it works is your bovine thrombin directly activates fibrinogen and converts it into fibrin monomers. So you can see that this works in a completely different place within the clotting cascade. It works down here in the common pathway bypassing all of the other necessary clotting factors. You do however have to have functional fibrinogen in order for this to work. The product Floseal™ itself is a little bit different from just using topical thrombin plus Gelfoam ® because the gelatin granules have been cross linked in such a way that they do not swell to nearly the same extent. It is absorbed in approximately 6-8 weeks.

Fibrin sealants are the last class of the hemostatic agents that I am going to address. Commercially it comes in many forms including tisseal and crosseal and there are many variations on the idea of fibrin sealants. One of those basic ideas is that you take pure human fibrinogen and combine it with bovine thrombin and they usually throw in an antifibrinolytic agent into the mix as well. So the way this works is that we take the bovine thrombin, it then converts this exogenous human fibrinogen to fibrin monomers, but you do need intrinsic, you need the patient's own factor XIII and calcium, which then converts it into fibrin polymer. In addition, they usually add an antifibrinolytic agent to the mix as well in order to stabilize the clot. So this does require functional factor XIII and calcium in order for these fibrin sealants to work. They are absorbed within 10-14 days and need a relatively dry field in order to work.

I am going to briefly mention some of the other classes of agents which are out there, but I am not going to address these in detail. There are some completely autologous fibrin sealants. The patient's own serum is taken and the fibrinogen and thrombin are purified. This achieves essentially the same effect as the fibrin sealants previously mentioned. There are a target platelet gels where again you purify the platelet with plasma and the patient's own serum combined with thrombin and you get similar agent to the fibrin sealants only there are some additional benefits: you do have some platelet direct growth factors involved which help with wound healing. There are some completely synthetic agents, which are made from polyethylene glycol gels that when you combine them make a completely synthetic hydrogel. Another product is bovine serum plus albumin plus glutaraldehyde, and poly N-acetyl glucosamine is something that the military is investigating as a hemostatic agent and it is a seaweed-based agent. This is just an idea of what is out there in addition to the agents I addressed previously.

Gelfoam ® and Surgicel, work here very proximally in the intrinsic coagulation pathway via contact activation. Collagen also works via contact activation, but also activates platelets. In a completely separate class we have agents that work in the common pathway, which includes Flowseal™, which is essentially topical thrombin and as well as fibrin glue and its variants.

Safety, three things to remember that Gelfoam® swells and it swells a lot. This has proven to be a problem when used within confined spaces such as the spinal foramina where in it can cause spinal cord nerve compression and brain compression.

Surgicel, of note, even though it does have an antimicrobial effect relative to the other hemostatic agents, it is still a nidus for infection. Avitene®, and in fact all of these agents, do cause a certain amount of foreign body reaction and granulation formation. But Avitene® has been found to be the worst offender in this way. You can see in this particular slide, they have the Avitene® cavity here, and then a large amount of surrounding edema and a foreign body reaction with giant cells here surrounding the Avitene®. In this picture you can see the periodic nature of Avitene® under polarized light. In fact, the manufacturers recommend that you apply these agents, then hold pressure and wait a while for a clot to form and then you remove the agent afterwards so that you do not leave it within the cavity in order to try to prevent foreign body reaction as much as possible. In addition, Avitene® because it comes in a light fluffy form, has been known to occasionally cause arterial embolization and it had been reported that it is causing laryngospasm when used in tonsillectomy. Collagen sponge has many of the same side effects as any of the bovine derived agents because there are known allergic reactions to some of these bovine antigens, which are containing these agents.

Floseal™ again as I mentioned before has much less swelling than the Gelfoam so it can be used within some of the more enclosed spaces. Because it is Gelfoam beads it can cause arterial embolization if it is used near a larger vessel. In fact Gelfoam beads

themselves have been used in order to embolize arterial malformation. Because it contains bovine antigens, it can have antibody formation, which I am going to talk about a little bit more in detail later. Some of the fibrin sealants use pooled human fibrinogen, in which there is always the potential for transmission of infectious agents. Also again, risks of arterial embolization and antibody formation.

Antithrombin antibodies: These are foreign antigens. A study of 200 patients showed 90% of those exposed to topical thrombin do have a transient elevation in IgG titers. Tadokoro et al in Japan also noted that you can have development of IgE antibodies. This can result in a prolonged thrombin time. Of note, thrombin time is actually a measure of fibrinogen count.

Thrombin time: the way this test was done, you add bovine thrombin to the patient's fibrinogen and see how long it takes for it to form a monomer. Because you have development of antibodies to bovine thrombin, you can have elevation in your thrombin time. This antibovine thrombin antibody can cross-react with human thrombin, but interestingly enough, this rarely ever causes any sort of clinical bleeding.

The real problem is with antifactor V antibody, as most commercial form of thrombin is contaminated with a certain amount of other bovine antigens and most importantly bovine factor V. So if you can get these antibovine factor V antibodies, which then cross-react with human factor V this can lead to a very severe coagulopathy and because this antibody can act as an inhibitor of factor V. On laboratory tests you can find a very decreased factor V level, increased PT and PTT, which does not correct when you add FFP and vitamin K. When you mix the patient's sera with a normal human sera, you do not get correction of the PT and PTT which suggest that it is not a cofactor deficiency, but it is actually an inhibitor causing the problem. So as you can see here the factor V is an activator of the conversion of prothrombin to thrombin and this is where you end up with problems. The same study noted that 50% of the 200 patients that they found that were exposed to topical thrombin did develop human factor V antibodies. The problem usually does not happen on the initial exposure, but it is when they are exposed again in the later point to the topical thrombin is when the potential for coagulopathy is exposed. Fortunately these IgG titers do fall off rapidly three to four weeks after the exposure and the treatment if you do encounter this is steroids, cyclophosphamides, IVIG plasmapheresis and platelet transfusion. Of note, I did not see actually any reports of this in the head and neck literature per se; most of the case reports of these events are in the cardiovascular and vascular literature.

Another requirement of a good hemostatic agent is efficacy. Basically there have been lots of studies both in vitro and in vivo using various animal models as well as human studies comparing these various hemostatic agents. The general gist of them is that fibrin sealant work better than Floseal™ which is better than Avitene® and then the collagen sponge, Surgicel and Gelfoam® are essentially equivocal. They do work better than placebo but can barely differentiate efficacy between any of them. Of note, Floseal™ and Avitene® do cause more inflammatory reactions than the others.

Usability: Gelfoam®, Surgicel, Avitene® and these collagen sponge can be stored at the room temperature and are basically ready to use out of the box. Floseal™ does require two to five minute prep time, you combine the thrombin with calcium and combine that to the gelatin granules. Fibrin sealants on the other hand need to be kept in cold storage and thawed prior to usage; it depends on what company you are using and what type and the prep time can be anywhere up to 20-30 minutes. So it is something to keep in mind if you think you want to use fibrin sealant during your case you should be prepared ahead of time in order to do so.

Affordability: This is an average or sort of an idea of what the cost is for some of these agents. Gelfoam®, Surgicel, collagen sponges are relatively inexpensive in a $10-20 per individual piece, whereas Avitene®, Floseal™ and fibrin sealants are much more expensive.

Approvability: All of these agents are regulated through the FDA as a class III medical device, which means they are subjective to this medical device reporting systems so that the manufacturers are obligated to report to the FDA when an adverse event happens. In fact, in 2004 the FDA released notification to users about Gelfoam® and its swelling

and use in neurosurgical procedures because of the potential for paralysis.

Summary: These agents are of course not a substitute for meticulous surgical technique. However, they can help decrease OR time and postop bleeding. In my review of the literature I did not see any difference in use or in complications between children and adults. In the case that I presented initially, if you do have a patient who has a known bleeding disorder, a hematology consult obviously can be useful. Hemostatic agents are of limited use because you do have problems in the clotting cascade so they can help you with other more systemic hemostatic agents. Again, this is a summary of the specific agents that I addressed in this talk. The big thing is to remember about the individual ones. Gelfoam® swells, so lot of it is a mechanical effect and you really should not be using it within an enclosed bony cavity. Surgicel has a relative antimicrobial effect when compared to other hemostatic agents. Avitene® has the worst foreign body reaction of all of these particular agents. The collagen sponge has sort of the same problems because is contains bovine parts that do have some antigenetic potential. Floseal™ and fibrin sealants are the most effective. These are the ones that involve thrombin, but something to keep in mind is the potential for antibody formation. Fibrin sealants have a longer prep time and higher cost than some of the other agents.

Case Presentation:

J.D. is an 8-year-old female with a history of von Willebrand's disease who presented to the Texas Children's Hospital ER with epistaxis. It started approximately two hours prior to her arrival. She noted bleeding only from the right side and denied any sensation of blood trickling down the back of her throat.

She had been seen one week ago in the ER for epistaxis, at which time her bilateral nares were packed with gelfoam. She was also given Factor VIII concentrate by the hematology service.

Her home medications included Amicar (aminocaproic acid) as needed for episodes of bleeding.

On examination, she had dried blood in her right nares with a small amount of oozing from the right anterior septum. No blood was noted in her left nares or oropharynx.

Hematology again recommended Factor VIII infusion. Floseal was placed in her right nares. No further bleeding was noted over the ensuing hour. She was given nasal saline and bacitracin for two weeks and was discharged home with outpatient follow-up.

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